Users Guide to Designing N-of-1 Trials

Chapter 3

Financing and Economics of Conducting n-of-1 Trials

Draft for Comment

The use of n-of-1 trials to improve therapeutic decision-making and clinical outcomes has been studied and reported upon for over 25 years. Selected reports indicate the approach can resolve therapeutic uncertainty in specific patients when the underlying condition and drugs are amenable to the n-of-1 approach. In a time of increasing interest in personalized medicine, the n-of-1 trial presents a potentially feasible and cost effective method of determining the best therapeutic option for a particular person. As patients and clinicians recognize that an individual's response to a medication may not be well represented by a population mean, the use of n-of-1 trials to distinguish true responses would seem logical. Nonetheless, after more than 25 years of sporadic reports on n-of-1 trials, largely from persons working in academic settings, to our knowledge the service is not generally available to patients and doctors in any country. This chapter will explore what is understood about costs, benefits, and possible financing of n-of-1 trials based on the literature and the authors' (WDP, EBL) experience.

While health care providers have access to an array of tools that lend a high degree of confidence to diagnoses, few if any widely available tools help providers determine which medication (or behavioral health treatment) is best for a patient. Providers rely on several imperfect strategies for therapeutic decision making. First, they interpret the evidence available from randomized controlled trials, which present the average benefits and risks of a particular drug. Relying on this evidence requires clinicians to find and interpret a sometimes large number of studies, then assess the ways in which their patient differs from the narrow population that qualified for inclusion in the study[1] and the degree to which the benefits and risks matter to that patient.[2] Second, clinicians may adopt a "trial of therapy" approach, in

which they start a patient on a drug and wait to see how it works. The biases and, thus, potential problems of this approach have been well described.[2-4] At times, clinicians may simply give patients two or more drugs in a similar class to take home and try at the patient's convenience (essentially an open label n-of-1 trial without any control for washout periods, placebo effect, or numbers of crossovers required for clinical decision making). The therapeutic decisions that result from these methods are imperfect, at best, and at worst may lead to unnecessary costs and higher than necessary rates of adverse effects.

Beyond improving initial therapeutic decision making, an n-of-1 trial has a number of potential longer-term benefits. In theory, the method should improve the risk-benefit ratio of a drug because the medication would be used only in people for whom there has been demonstrated effectiveness. Short term side effects are typically clearly demonstrated in n-of-1 trials. Long-term adverse events, however, are not immediately available and would need to be factored into a risk-benefit model using population based data. Current population-based information may make it difficult to extrapolate the full benefit of medications in a heterogeneous population. n-of-1Sub-analyses of defined responders can help overcome some of these issues, but studies are often not large enough for these sub-analyses nor are data available at the patient level across studies to allow others to examine the heterogeneity issue. N of 1 trials eliminate the concern about population-based heterogeneity of responses when they can be carried out.

Reach of the n-of-1 Method

Despite the many potential benefits, n-of-1 trials have not made it into mainstream clinical medicine[5] and to our knowledge have never been a covered benefit in any insurance plan (private or government run) in the United States or Canada. A 2010 systematic review found 108 unique trial protocols from the years 1986 to 2010, and the majority had authors from Canada (35%), Europe (26%), and the United States (22%).[6] n-of-1 trial services have been run almost exclusively out of academic centers with little reach into community practice in the US; somewhat broader reach has been achieved in Australia.[7] As academically run services, most have been supported by grants and local institutional funds. Gabler et al.'s systematic review found that most trials (69%) reported receiving Institutional Review Board (IRB) approval and 56 trials (52%) received funding.[6] No articles reported charging patients or insurance companies for the service. The involvement of IRBs in the majority of trial activities indicates the low acceptance of these activities as a component of routine clinical care. A more complete discussion of the ethics of n-of-1 trials is presented in Chapter 2. Considering just the impact on financing, the need for IRB review further highlights the "experimental" nature of the process and makes insurance coverage less likely as insurance rarely pays for research activities.

Cost Data for n-of-1 Trials

While there is no literature on third party or patient payments for n-of-1 trials, three articles have explored the costs of conducting trials (see Table 1). The reported costs vary widely, partly perhaps due to differences in costs between countries (one article from the US, one from Canada, and one from Australia) as well as inflationary differences (1993 US dollars

versus 2008 Canadian dollars, for instance). Beyond these variables, there are different approaches advocated for conducting n-of-1 trials. Many trial centers develop new trial instruments for each patient, based on the patient's stated preference or importance of one symptom or sign over another. Others report on multiple trials based around a single clinical question, using a standardized set of assessment instruments. Some trials provide feedback to the referring physician who is expected to develop a treatment plan with the patient based on the trial results. Others incorporate this discussion into the trial itself. These and other differences in approaches would be expected to impact the overall cost of a single trial. In this report, we do not attempt to standardize costs to a particular reference point but simply express costs as reported in the papers we found.

Costs have been evaluated in detail by Scuffham et. al. related to two multi-patient n-of-1 trial series conducted by the University of Queensland.[8] Using classic economic approaches they initially divided costs into fixed start-up costs and variable per patient or per trial costs. The costs were considered within the context of a "research" activity conducting two groups of n-of-1 trials using the same medications for each study set, the same outcome and side effect instruments for each group of studies, and the same patient problems for each group of studies. The research approach clearly affected the kinds of costs incurred and may have impacted whether some costs were considered fixed or variable. In this context the following items were considered fixed costs:

- Seeking funding
- Developing the research protocol
- Obtaining ethical review

- Developing instruments/forms for data collection
- Developing treatment sequencing
- Blinding medications
- Design/preparation of medication packs
- Database development

Variable costs were categorized as follows:

- Patient recruitment
- Managing the operation of each trial
- Data collection
- Data analysis
- Generation of results and feedback to clinicians and/or patients

The Queensland trial service found a total fixed cost of $23,280 Australian (2005 Australian dollars) to set up two different n-of-1 trial protocols. Various components of these costs would not be applicable when operating n-of-1 trials primarily for clinical purposes. For example, the cost analysis included as "fixed costs" the costs of applying for grant funding and the costs of applying for ethical approval, which accounted for $7730 or 33% of the total start-up costs. While patient recruitment could also be considered a "research" expense, one would imagine that a commercially available n-of-1 trial system would incur marketing costs, which would likely markedly exceed the relatively low "recruitment costs" assigned to this analysis. The cost of preparing medications is listed as a fixed cost, though if medication acquisition costs

were included this would more logically be a variable cost. The investigators considered the developed protocols to be reasonably applied to 200 people each with resultant fixed costs per patient of $116. Variable costs were $610 for a trial of celecoxib versus long acting acetaminophen and $577 for a trial of gabapentin versus placebo. The overall cost per trial based on this study is in line with many other diagnostic tests. This trial did not include costs related to the development of an electronic data collection system, which would be essential for any present-day commercial or clinically-based system in the US or Canada. Even though development of a robust electronic data collection system could run into the hundreds of thousands of dollars (US), if the system were used for enough trials the overall cost per patient could still be kept in line with complex diagnostic tests such as advanced imaging modalities.

N-of-1 trials performed outside of a research study can provide further insight into the costs of the method. One of this chapter's authors (EBL) worked with colleagues to explore the costs of operating an n-of-1 trial service in an academic institution. This service was operated for clinical purposes and therefore did not "recruit" patients as a research protocol would. After initial interactions with the local Institutional Review Board (IRB), the service was declared to be a component of clinical care, therefore not requiring IRB review of each new trial protocol.

Larson's group designed each single patient trial in their series individually. Their cost assessment then focused on assessing the direct costs of operating a single trial. They estimated 16.75 hours of staff time per trial, which included a physician lead, nursing, data entry, analysis and feedback time. Of note, none of the staff were solely devoted to work on trials but charged time to the n-of-1 trial service alongside of other job tasks. In 1990 US dollars

this was estimated at approximately $500/study plus the cost of the medications. In 2013 dollars, just the staff time would likely rise to between $1500 and $2000.

An additional experience comes from a commercial application of the n-of-1 model. One of the authors (WDP)worked as an independent evaluator for a commercial venture that sought to bring n-of-1 trials to clinicians commercially, in a much more automated form. The group developed a web-based data collection system and used a validated set of symptom and side-effect questionnaires for the drugs they offered for study. They offered all three primary types of n-of-1 trials, active versus placebo, active drug A versus active drug B, and Dose A versus Dose B of the same drug. The system allowed clinicians to simply write a prescription for the study of interest, from a predetermined set of medications. The company contacted the patient and established a secured web account. A contracted pharmacy prepared the medication unit dose packs with over encapsulation. The initial medications available for study were H2 blockers, proton pump inhibitors and anti-histamines. The underlying study design was set, by default, as a five cross-over pairs design for all studies. The number of days per cross-over was determined by the longest half-life of the medications under study allowing for adequate time to assess symptoms and side effects after a wash out period for each medication. If two active comparator drugs were used, patients were always on active drug but information from a pre-determined wash out period was ignored. A randomly selected cross-over pattern was sent to the pharmacy to prepare the medications for each participant. Analytics were built into the database as a report feature. Clinicians could receive reports as a hard copy or log in to the web site for the information including which medication improved symptoms the best, which had lower side effect profiles and if versus a placebo if there was a clinically meaningful effect.

The evaluation of the system was stopped early due to financial problems. Prior to that, 64 patients were enrolled altogether; 34 patients were enrolled in one of two n-of-1 drug comparison groups, but only three patients completed their full evaluations. Qualitative feedback indicated that patients did not see enough value in the added certainty provided by the trial results, given that they needed to complete daily symptom and adverse event logs for over two months. Patients indicated they could easily conduct their own, open label, trials quickly and inexpensively to determine which medication worked best for them. This finding may have been influenced by the fact that all the medications being studied became available over the counter by the time the evaluation was underway. Interestingly, the side effect rates (which study data showed were clearly caused by the medication in question, based on study completers or partial completers) were much higher than reported in the literature or package inserts for the medications. This experience is consistent with reports of greater side effects when drugs are approved by FDA and used in the more general population compared with the highly selected persons typically enrolled in studies meeting FDA efficacy standards.

Cost Offset

Scuffham et. al. examined the cost offsets from two n-of-1 trials using data from the Queensland, Australia, multi-patient n-of-1 trials examining the use of cox-2 inhibitors versus acetaminophen for osteoarthritis, and gabapentin versus placebo for neuropathic pain.[8] In both trials the n-of-1 arms of the study ended up costing more per patient then the usual care groups even including cost savings from individuals who were able to stop taking ineffective medications. This finding could potentially be due to the small differences in outcomes

between the n-of-1 and usual care groups and the low responder rates for both active medications – 17% for celecoxib and 24% for gabapentin in the n-of-1 trial groups. Nonetheless, the variables most responsible for cost differentials could be calculated. These included the underlying variable costs of conducting n-of-1 trials, the number of individuals among whom the fixed costs are shared, the probability that the n-of-1 trial will result in use of the study medication, the time horizon for which the results are valid, and the cost differential of the medications being studied. The longer the patients in this report were credited with taking medication of no value or causing undesirable side effects, the more value would issue from an n-of-1 trial, implying greater cost effectiveness. The paper examined time horizons of five years and lifetime, though other studies indicate time horizons of less than one year following n-of-1 trials.[9,10] The model also indicates that the greater the effect differences between two medications or medication and placebo, the greater the cost efficacy of n-of-1 trials. This analysis used an imputed usual care group and as such may not entirely capture the impact of an n-of-1 trial at the patient level if a higher percent of people remain on an ineffective drug than imputed. n-of-1

In examining other reports of multi-patient n-of-1 trials it is evident why cost offsets can be hard to demonstrate. In the Queensland trials the pain differences for the n-of-1 trial participants versus usual care at the end of the each trial was .28 points on a 10-point scale while the gabapentin trial demonstrated a .11 drop in pain compared to the usual care group.[11,12] Similarly, in a study of theophylline in patients with COPD, Mahon et. al. found that in 68 patients randomized to an n-of-1 trial versus usual care, 7 of the 34 n-of-1 trial patients benefited from theophylline, while 11 of 34 elected to continue theophylline at 3 months

(35%).[9] By the end of the trial at 12 months, 16 of 34 n-of-1 participants were using theophylline (47%). In the usual care group, where theophylline effectiveness was determined through open label on- off usage, 13 of 30 (43%) were using theophylline at 3 months and 15 of 30 (50%) were using theophylline at 12 months. Furthermore, there was no difference across study populations (responders and non-responders in both groups included in the intent to treat analysis) in chronic respiratory disease questionnaire scores or six-minute walk times.

In a study of the use of non-steroidal anti-inflammatory medications (NSAIDs) in osteoarthritis, Pope et al. found no differences in use of NSAIDs between n-of-1 trial participants and usual care participants (81% n-of-1 versus 79% usual care).[10] This relatively small trial (N = 51) found no significant differences in an overall health assessment scale, osteoarthritis pain and function scale, or SF-36 scores between the two groups. The total costs of care (osteoarthritis treatment), including the n-of-1 trial, at six months was $551.66 +/- $154.02 n-of-1 trial versus $395.62 +/- $226.87 for the usual care group (2003 Canadian dollars). Since n-of-1 trials, even if taken to scale, will always cost more than open label clinical trials it will require demonstrations of greater effect from the trials themselves to demonstrate reasonable cost offsets.

Value Proposition

In general our review concludes that it has been difficult to demonstrate a value proposition for n-of-1 trials given the combination of limited differences in outcomes between n-of-1 participants and usual care, the tendency of both groups to end up with similar medication usage patterns over time, and the small sample size of all published trials. A more

general issue is that chronic disease effects and available treatments change over time. These underlying changes may make results of an individual treatment of little enduring value due to changes in symptom patterns or a patient's preference or physician recommendation based on availability of different treatments. For n-of-1 trials to be valuable in the face of seemingly inevitable changes would require that the methods be relatively straightforward and efficient and meet patients' timeliness expectations.

Karnon et al. have explored the use of n-of-1 trials to study the economic impact of various medication choices at the individual patient level.[13] The authors consider adding questions related to total cost of care, cost of alternative medications used and/or quality of life to better understand the cost/benefit of various medication choices. The paper considers the ethical issues of basing decisions on overall improvement versus the cost per unit of improvement. It concludes that clear preferences should drive clinical decisions and that economic considerations should only come into play when the clinical decision is ambiguous. The use of a series of n-of-1 trials with additional data collection could help one more precisely understand the economic and quality of life impact of various medication choices in responders. This rationale could also arguably be applied to diagnostic tests, which are typically adopted and paid for without a clear demonstration of a value proposition other than improved diagnostic accuracy.

Influence of Personalized Medicine

Personalized medicine presents an area where n-of-1 trials may help us study outcomes for commonly prescribed drugs. With growing concern about the overall safety and risk-benefit

profile of many medications, n-of-1 trials could be used to personalize this information. n-of-1 trials seem particularly well suited to understanding side effects associated with a medication at the personal level. Could this drive interest in the method, if it was better understood? Similarly, n-of-1 trials are well suited to study herbal preparations and dietary supplements; There are many "natural" supplements available for a wide variety of conditions, most of which will never be submitted to rigorous population-level randomized controlled trials. Could a sub-group of individuals interested in trying supplements form a grass roots user group through crowd-sourcing and be interested in the therapeutic precision of n-of-1 trials? As we move towards personalized medicine based on genomic or proteinomic data, combining n-of-1 trials for appropriate conditions and medications may be the one rational way to study outcomes for both individuals (personalized medicine) and general populations using commonly prescribed drugs. We can assume that the attractiveness of personalized medicine will grow and as science-based personalized medicine disseminates, n-of-1 trials seem elegantly suited to be part of personalized medicine.

Potential Financing Options

We have identified a number of potential ways in which the n-of-1 trial could be paid for. It is conceivable that large pharmacy chains could take on the conduct of n-of-1 trials. Most of these companies already have a strong Internet and mobile presence, the ability to prepare the medications for trials, and established financial relationships with payers.

If positive financial offsets for selected medications were demonstrated, would Accountable Care Organizations (ACOs) consider contracting with commercial vendors or

pharmacy chains for the service for selected medications? It is conceivable that with ACOs and cost bundling, n-of-1 trials would have a value proposition as a strategy to manage expenses while reducing side effects and adverse effects of drugs, especially commonly used or expensive drugs. n-of-1 trials can be considered a cognitive service. Cognitive services do not involve a capital investment in a machine or device or provision or a procedure and thus have little potential in a fee for service world to generate fees to cover implementation or facility costs.

In addition, up to now no self-interested group has been inclined to develop a business case for n-of-1 trials. If anything, pharmaceutical companies have previously had a disincentive in a fee for service world to consider n-of-1 trials, since these trials typically lead to results which reduce overtreatment and highlight side effects. In an ACO world, n-of-1 trials could be part of a risk mitigation strategy to reduce overtreatment, excess costs, and side effects. Given the precision of information on short term side effects developed through n-of-1 trials and the current FDA priority to find better ways of detecting adverse effects post marketing and in general, the FDA might consider whether developing an infrastructure for an n-of-1 enterprise might be a worthwhile way to enhance assessment of medications in use for symptomatic treatment of chronic diseases. If a trial registry were available that contained both standardized methods and outcome assessment tool kits as well as a repository for trial results, this could be an added source of assessing benefit and risk of drugs in everyday populations through secondary analysis of the pooled results. We believe this idea is one worth exploring especially for medications that are likely to be taken long term for chronic conditions.

Innovations that May Increase the Appeal of n-of-1 Trials

Several innovations could increase the reach and appeal of n-of-1 trials. Interactive technology (discussed in Chapter 5 of this monograph, which covers information technology) could integrate patient preferences (a potentially variable cost) while still maintaining a "standard" data collection format. Validated instruments, for both outcomes and adverse effects, could be built into to the data collection system with patients picking the most important outcome as well as the side effects they consider least tolerable or most troublesome. While the initial costs of development could be substantial, the per trial cost could still be reasonable if amortized over thousands of patients. Overall usage of the n-of-1 trials would need to expand greatly for this model to be cost effective.

As mentioned, a national n-of-1 trial registry could improve shared decision making based on an individual n-of-1 trial over time. Such a registry would store and analyze the combined results of n-of-1 trials using standardized processes and contain well developed assessment methods and outcome scales for appropriate medications, particularly those with narrow therapeutic windows, moderate population level efficacy, or high cost to benefit ratios. This advance would increase the reach and use of n-of-1 trials greatly (but would likely require substantial ongoing support).

Conclusion

The long term financing of n-of-1 trials will be determined by a value proposition that is more attractive to patients, clinicians, other providers including perhaps pharmaceutical companies, payors, and possibly regulators. Presently the limited spread of n-of-1 trials likely reflects that the value proposition, especially in a fee for service world and a world where rapid

availability of information is prized. n-of-1 trials, with their prolonged timeframe to conduct, are relatively unattractive compared to other clinical activities that produce rapid results, but could essentially change the way that medicine is practiced. Can n-of-1 trials become more standardized, more efficient, and more patient and physician friendly? Most importantly, can they be moved from the rarefied world of the academic medical center and faculty with keen interests in clinical epidemiology and research to the everyday world of clinical practice and consolidating delivery systems? Larger scale, more efficient services aimed at enhancing patient centered outcomes through more precise therapeutics could be a way to demonstrate value. The outcomes of greatest interest would be improved effectiveness of treatment, reduced side effects, and improved patient and physician satisfaction along with reduced or improved management of costs through avoidance of adverse events and an ability to use less expensive drugs of proven effectiveness for individual patients.

As with diagnostic interventions, an understanding of the characteristics of the intervention is important in determining when it will benefit patients and when it is contraindicated. For diagnostic interventions these characteristics include specificity, sensitivity, prior probabilities and positive and negative predictive values. For n-of-1 trials a better understanding of the impact of different characteristics of the treatment differentials would help advance the concept. For instance, what is the impact of different levels of percent of positive responders on the utility of a n-of-1 trial? At what level of population response is an n-of-1 trial no longer indicated? What is the impact of various levels of cost differentials of the final treatments on the potential benefits of an n-of-1 trial? Clinicians need information that will help them understand where n-of-1 trials would be of most value.

Overall, we conclude that the limited data currently available suggest that n-of-1 trials can be conducted for a reasonable per patient cost (not considering the cost of the drug or drugs to be tested) and that these costs could be further lowered with modern technology. Furthermore, modern technology should be able to blend standardized data collection instruments with patient preference and modern testing theory to limit data collection from non-useful questions for a particular patient. The value proposition, from both the financial and patient outcome perspectives, is where the most uncertainty exists at present. Until this value proposition is better defined it is unlikely that commercial payers will include coverage for n-of-1 trial activities.

Table 1 Fixed and Variable Costs from Published n-of-1 Trials

Drug	Ref	Country/ Currency	Year of Study	Fixed Costs/ # of studies	Variable Costs/ patient	Cost Diff (Nof1 minus control)/ patient/ time
Various	Larson	USA	1990	$500/ study	Not reported	Not reported
NSAIDs	Pope[10]	Canada	2002-2003	Not reported	Not reported	$31.91/6 months
Celecoxib	Scuffham[8]	Australia	2003-2005	$23,280/ 200 patients	$1,257	$39/12 months
Gabapentin	Scuffham[8]	Australia	2003-2005	$23,280/ 200 patients	$1,322	$876/ 12 months

Checklist

Guidance	Key Considerations	Check
Consider the cost related to assessment instruments.	• Developing new for each patient/trial increases costs • Standardized assessments reduce analytic efforts later.	☐
Provide feedback.	• Feedback to clinicians will help them develop treatment plans • Feedback can be incorporated into the trial itself	☐
Plan for fixed start-up costs.	• Fixed costs include developing instruments/forms for data collection, developing treatment sequencing plans, blinding medications, designing and preparing medication packs, developing a database, marketing the trials	☐
Think about additional costs if your service will be considered "research."	• Research costs include seeking funding, work of completing IRB process, more complicated consent	☐
Plan for variable per patient or per trial costs.	• Variable costs include recruiting patients, managing the operation of each trial, collecting data, analyzing data, generating results and feedback to clinicians and/or patients	☐
If considering the cost offset, think about elements that have been shown to affect that.	• The greater the effect differences between two medications or medication and placebo, the greater the cost effectiveness • The longer the patients take medication of no value or which causes undesirable side effects, the more value would issue from an n-of-1 trial, implying greater value and thus cost effectiveness	☐

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